

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

| | |
|--|--|
| Date of mailing (day/month/year) 16 July 1999 (16.07.99) | |
| International application No. PCT/EP98/07792 | Applicant's or agent's file reference S-30287/A |
| International filing date (day/month/year) 01 December 1998 (01.12.98) | Priority date (day/month/year) 03 December 1997 (03.12.97) |
| Applicant ATKINSON, Howard, John et al | |

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

10 June 1999 (10.06.99)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|--|--|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer F. Baechler Telephone No.: (41-22) 338.83.38 |
|--|--|

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

| | |
|--|---|
| Date of mailing (day/month/year) 20 September 1999 (20.09.99) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference S-30287/A | |
| International application No. PCT/EP98/07792 | International filing date (day/month/year) 01 December 1998 (01.12.98) |

1. The following indications appeared on record concerning:

☒ the applicant
 ☐ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address

NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT M.B.H.
Brunner Strasse 59
A-1235 Vienna
Austria

State of Nationality

AT

State of Residence

AT

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

Name and Address

NOVARTIS-ERFINDUNGEN
VERWALTUNGSGESELLSCHAFT M.B.H.
Brunner Strasse 59
A-1230 Vienna
Austria

State of Nationality

AT

State of Residence

AT

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

The postcode has changed. Please also note the change in the agent's address, as indicated in the addressee box above.

4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned
☐ the International Searching Authority
 ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority
 ☐ other:

| | |
|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35 | Authorized officer S. De Michiel Telephone No.: (41-22) 338.83.38 |
|---|---|

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BECKER, Konrad
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
CH-4002 Basel
SUISSE

| | |
|--|---|
| Date of mailing (day/month/year) 28 April 2000 (28.04.00) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference S-30287/A | |
| International application No. PCT/EP98/07792 | International filing date (day/month/year) 01 December 1998 (01.12.98) |

1. The following indications appeared on record concerning:

☒ the applicant
 ☒ the inventor
 ☐ the agent
 ☐ the common representative

Name and Address

 ATKINSON, Howard, John
 43 Sutherland Avenue
 Leeds LS8 1BY
 United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

Name and Address

 ATKINSON, Howard, John
 Coach House
 Stainforth
 Nr Settle BD24 9PH
 N. Yorkshire
 United Kingdom

State of Nationality

GB

State of Residence

GB

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned
☐ the International Searching Authority
 ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority
 ☐ other:

 The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

S. De Michiel

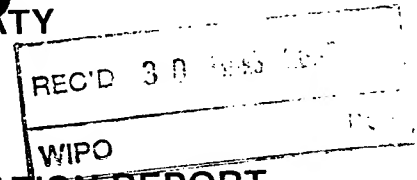
Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



16

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|---|--|---|--|
| Applicant's or agent's file reference S-30287/A | | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP98/07792 | International filing date (day/month/year) 01/12/1998 | Priority date (day/month/year) 03/12/1997 | |
| International Patent Classification (IPC) or national classification and IPC C12N15/82 | | | |
| Applicant NOVARTIS AG et al. | | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand 10/06/1999 | Date of completion of this report 27. 03. 00 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer A. M. Merlos Telephone No. +49 89 2399 8559  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/07792

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.)*:

Description, pages:

1-32 as originally filed

Claims, No.:

1-17 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------|-----------------------------|
| Novelty (N) | Yes: | Claims 4, 5, 6, 9-11 |
| | No: | Claims 1, 2, 3, 7, 8, 12-17 |
| Inventive step (IS) | Yes: | Claims 9-11 |
| | No: | Claims 1-8, 12-17 |
| Industrial applicability (IA) | Yes: | Claims 1-17 |
| | No: | Claims |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP98/07792

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/07792

- 1.1 With respect to document WO 96/10083, claims 1, 2, 7, 13 and 15-17 appear not to conform with the requirements of Art. 33(2), (3) PCT. Said document describes the recombinant production of fusion proteins optionally linked by a linker region for the purpose of protecting plants against insect pests (see pages 3 and 4, 6 and 7, in particular Example 22 and part of the claims).
Alternatively, with respect to documents EP-0 497 366 and WO 94/13810, it would appear that claims 1, 2, 3, 6, 7, 8 and 12-17 do not refer to novel and/or inventive subject-matter.
WO 94/13810 discloses the construction of proteinase inhibitor fusion proteins linked via a protease sensitive linker so that upon expression in a plant transformed with said construct, the plant proteinases cleave the fusion molecule. The fusion protein should increase, enhance or facilitate in plants, the resistance to insects or other pathogens (see page 8, line 15 to page 12, line 31, claims). Document EP-A-0 497 366 describes the construction of so-called "bridged" oligopeptides to protect plants against microbial pathogens (see page 5, last paragraph, pages 7 and 16-21).
At present, claims 1-3, 6-8, and 12-17 are too generally drafted and lack any particular features which would render the matter claimed clearly novel and/or inventive with respect to the prior art.
- 1.2 It is further noted that document WO 96/16173 refers to the development of modified and/or hybrid proteinase inhibitors which are more effective in making plants nematode-resistant. The use of such hybrid proteinase inhibitors in the method as claimed in claims 1-4, 7, 12 and 17, the fusion proteins and transgenic plants expressing them and the corresponding DNA molecules encoding these hybrids (claims 13-16) therefore appear obvious. Said claims are therefore regarded to lack an inventive aspect according to (Art. 33(3) PCT).
This is also true for claim 5 wherein the method particularly refers to CpTI, insofar as the cowpea trypsin inhibitor (CpTI) was already known to have anti-nematode activity (see WO92/15690).
- 2). The expression "preferentially" used in claim 6 raises unclarity whether the claim is limited to a root-specific promoter or not.
- 3). In case of an unvalid priority of 03.12.1997, intermediate document "Urwin et al., Planta, vol. 204, April 1998, pages 472-479" may become relevant when the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP98/07792

application enters the european phase.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|--|--|
| Applicant's or agent's file reference S-30287/A | FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small> | |
| International application No. PCT/EP 98/ 07792 | International filing date (day/month/year) 01/12/1998 | (Earliest) Priority Date (day/month/year) 03/12/1997 |
| Applicant NOVARTIS AG et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

EP 98/07792

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/82 C12N15/52 C12N15/53 C12N9/00 C12N9/02
 C12N5/10 G01N33/50 A01H5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 96 10083 A (CIBA GEIGY AG) 4 April 1996 page 3,6; example 22 --- | 1,2,7, 13,15-17 |
| X | EP 0 497 366 A (DONEGANI GUIDO IST) 5 August 1992 pages 5,6-15,16; page 18, line 43-50; claims --- | 1,2,8, 13,15-17 |
| Y | WO 96 16173 A (UNIV LEEDS ; ATKINSON HOWARD JOHN (GB); MCPHERSON MICHAEL JOHN (GB)) 30 May 1996 pages 1,3,4,5,; page 6, line 16-20; page 11,22-30; claims 27-38; Table 3 --- -/-- | 1-4,7, 12-17 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 March 1999

Date of mailing of the international search report

13/04/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Holtorf, S

INTERNATIONAL SEARCH REPORT

International Application No.

P 98/07792

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 94 13810 A (UNIV MELBOURNE ;ANDERSON MARILYN ANNE (AU); ATKINSON ANGELA HILARY) 23 June 1994 | 1-3,7, 13-17 |
| Y | see page 4 | 1-4,6,7, 12-17 |
| Y | --- WO 97 20057 A (NICKERSON BIOCEM LTD ;ATKINSON HOWARD JOHN (GB); LILLEY CATHERINE) 5 June 1997 page 7,8,11; example 3,4,5; claims | 6 |
| A | --- WO 92 15690 A (NICKERSON BIOCEM LTD) 17 September 1992 pages 6,7,9,10; examples 1,6 | 1-17 |
| A | --- LILLEY,C.J., ET AL. : "characterization of intestinally active proteinases of cyst nematodes" PARASITOLOGY, vol. 113, no. Pt4, October 1996, pages 415-425, XP002097967 abstract; page 416,417,420,423, left column | 1-17 |
| A | --- URWIN P E ET AL: "RESISTANCE TO BOTH CYST AND ROOT-KNOT NEMATODES CONFERRED BY TRANSGENIC ARABIDOPSIS EXPRESSING A MODIFIED PLANT CYSTATIN" PLANT JOURNAL, vol. 12, no. 2, 1997, pages 455-461, XP000198746 page 459, right column | 1-17 |
| P,X | --- URWIN, P.E., ET AL.: "enhanced transgenic plant resistance to nematodes by dual proteinase inhibitor constructs" PLANTA, vol. 204, April 1998, pages 472-479, XP002097968 see the whole document ----- | 1-10,12, 13,15-17 |
| | | |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07792

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| WO 9610083 | A | 04-04-1996 | US 5849870 A | 15-12-1998 |
| | | | AU 692934 B | 18-06-1998 |
| | | | AU 3743395 A | 19-04-1996 |
| | | | BG 101384 A | 31-10-1997 |
| | | | BR 9509099 A | 30-09-1997 |
| | | | CA 2199049 A | 04-04-1996 |
| | | | CN 1160420 A | 24-09-1997 |
| | | | EP 0792363 A | 03-09-1997 |
| | | | HU 77449 A | 28-04-1998 |
| | | | JP 10506532 T | 30-06-1998 |
| | | | US 5872212 A | 16-02-1999 |
| | | | US 5770696 A | 23-06-1998 |
| | | | US 5840868 A | 24-11-1998 |
| | | | US 5866326 A | 02-02-1999 |
| | | | US 5877012 A | 02-03-1998 |
| | | | ZA 9508121 A | 29-04-1996 |
| EP 0497366 | A | 05-08-1992 | AU 648140 B | 14-04-1994 |
| | | | AU 1065092 A | 06-08-1992 |
| | | | CA 2060455 A | 02-08-1992 |
| | | | JP 5294995 A | 09-11-1993 |
| | | | US 5519115 A | 21-05-1996 |
| WO 9616173 | A | 30-05-1996 | AU 3877095 A | 17-06-1996 |
| | | | CA 2205356 A | 30-05-1996 |
| | | | EP 0793722 A | 10-09-1997 |
| | | | JP 10510146 T | 06-10-1998 |
| WO 9413810 | A | 23-06-1994 | AU 680855 B | 14-08-1997 |
| | | | AU 5689194 A | 04-07-1994 |
| | | | CA 2151933 A | 23-06-1994 |
| | | | EP 0674712 A | 04-10-1995 |
| | | | JP 8506482 T | 16-07-1996 |
| | | | NZ 258824 A | 24-11-1997 |
| WO 9720057 | A | 05-06-1997 | AU 7702496 A | 19-06-1997 |
| | | | CA 2238943 A | 05-06-1997 |
| | | | EP 0871752 A | 21-10-1998 |
| WO 9215690 | A | 17-09-1992 | AT 160175 T | 15-11-1997 |
| | | | AU 665530 B | 11-01-1996 |
| | | | AU 1353192 A | 06-10-1992 |
| | | | CA 2107234 A | 06-09-1992 |
| | | | DE 69223080 D | 18-12-1997 |
| | | | DE 69223080 T | 25-06-1998 |
| | | | EP 0502730 A | 09-09-1992 |
| | | | ES 2111041 T | 01-03-1998 |
| | | | GR 3026133 T | 29-05-1998 |
| | | | US 5494813 A | 27-02-1996 |

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP 98/07792

International Application No.

01 DEC 1998

(01.12.1998)

International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) S -30287/A

| | |
|---|---|
| Box No. I TITLE OF INVENTION | |
| Proteinase Inhibitor Fusion Proteins | |
| Box No. II APPLICANT | |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) | |
| Novartis AG Schwarzwaldallee 215 4058 Basel CH | |
| <input type="checkbox"/> This person is also inventor | |
| Telephone No. +41 61 324 11 11 | |
| Facsimile No. +41 61 322 75 32 | |
| Teleprinter No. | |
| State (that is, country) of nationality: CH | State (that is, country) of residence: CH |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input checked="" type="checkbox"/> the States indicated in the Supplemental Box | |
| Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) | |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.) | |
| Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1235 Vienna AT | |
| This person is: <input checked="" type="checkbox"/> applicant only <input type="checkbox"/> applicant and inventor <input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.) | |
| State (that is, country) of nationality: AT | State (that is, country) of residence: AT |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input checked="" type="checkbox"/> the States indicated in the Supplemental Box | |
| <input checked="" type="checkbox"/> Further applicants and/or (further) inventors are indicated on a continuation sheet. | |
| Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE | |
| The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: <input checked="" type="checkbox"/> agent <input type="checkbox"/> common representative | |
| Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) | |
| BECKER, Konrad Novartis AG Patent- und Markenabteilung Lichtstrasse 35 4002 Basel CH | |
| Telephone No. +41 61 324 11 11 | |
| Facsimile No. +41 61 322 75 32 | |
| Teleprinter No. | |
| <input type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent. | |

Continuation of Box No. III

FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

ATKINSON, Howard John
43 Sutherland Avenue
Leeds LS8 1BY
GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MCPHERSON, Michael John
45 Henley Avenue
Thornhill, Dewsbury WF12 OLN
GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

URWIN, Peter Edward
86 Swinnow Close
Bramley, Leeds LS13 4NF
GB

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
☐ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☒ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line).....

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | | |
|---|--|--|--|
| <input checked="" type="checkbox"/> AL | Albania..... | <input checked="" type="checkbox"/> LS | Lesotho..... |
| <input checked="" type="checkbox"/> AM | Armenia..... | <input checked="" type="checkbox"/> LT | Lithuania..... |
| <input checked="" type="checkbox"/> AT | Austria..... | <input checked="" type="checkbox"/> LU | Luxembourg..... |
| <input checked="" type="checkbox"/> AU | Australia..... | <input checked="" type="checkbox"/> LV | Latvia..... |
| <input checked="" type="checkbox"/> AZ | Azerbaijan..... | <input checked="" type="checkbox"/> MD | Republic of Moldova..... |
| <input checked="" type="checkbox"/> BA | Bosnia and Herzegovina..... | <input checked="" type="checkbox"/> MG | Madagascar..... |
| <input checked="" type="checkbox"/> BB | Barbados..... | <input checked="" type="checkbox"/> MK | The former Yugoslav Republic of Macedonia..... |
| <input checked="" type="checkbox"/> BG | Bulgaria..... | | |
| <input checked="" type="checkbox"/> BR | Brazil..... | <input checked="" type="checkbox"/> MN | Mongolia..... |
| <input checked="" type="checkbox"/> BY | Belarus..... | <input checked="" type="checkbox"/> MW | Malawi..... |
| <input checked="" type="checkbox"/> CA | Canada..... | <input checked="" type="checkbox"/> MX | Mexico..... |
| <input checked="" type="checkbox"/> CH und LI | Switzerland and Liechtenstein..... | <input checked="" type="checkbox"/> NO | Norway..... |
| <input checked="" type="checkbox"/> CN | China..... | <input checked="" type="checkbox"/> NZ | New Zealand..... |
| <input checked="" type="checkbox"/> CU | Cuba..... | <input checked="" type="checkbox"/> PL | Poland..... |
| <input checked="" type="checkbox"/> CZ | Czech Republic..... | <input checked="" type="checkbox"/> PT | Portugal..... |
| <input checked="" type="checkbox"/> DE | Germany..... | <input checked="" type="checkbox"/> RO | Romania..... |
| <input checked="" type="checkbox"/> DK | Denmark..... | <input checked="" type="checkbox"/> RU | Russian Federation..... |
| <input checked="" type="checkbox"/> EE | Estonia..... | <input checked="" type="checkbox"/> SD | Sudan..... |
| <input checked="" type="checkbox"/> ES | Spain..... | <input checked="" type="checkbox"/> SE | Sweden..... |
| <input checked="" type="checkbox"/> FI | Finland..... | <input checked="" type="checkbox"/> SG | Singapore..... |
| <input checked="" type="checkbox"/> GB | United Kingdom..... | <input checked="" type="checkbox"/> SI | Slovenia..... |
| <input checked="" type="checkbox"/> GE | Georgia..... | <input checked="" type="checkbox"/> SK | Slovakia..... |
| <input checked="" type="checkbox"/> GH | Ghana..... | <input checked="" type="checkbox"/> SL | Sierra Leone..... |
| <input checked="" type="checkbox"/> GM | Gambia..... | <input checked="" type="checkbox"/> TJ | Tajikistan..... |
| <input checked="" type="checkbox"/> HR | Croatia..... | <input checked="" type="checkbox"/> TM | Turkmenistan..... |
| <input checked="" type="checkbox"/> HU | Hungary..... | <input checked="" type="checkbox"/> TR | Turkey..... |
| <input checked="" type="checkbox"/> ID | Indonesia..... | <input checked="" type="checkbox"/> TT | Trinidad and Tobago..... |
| <input checked="" type="checkbox"/> IL | Israel..... | <input checked="" type="checkbox"/> UA | Ukraine..... |
| <input checked="" type="checkbox"/> IS | Iceland..... | <input checked="" type="checkbox"/> UG | Uganda..... |
| <input checked="" type="checkbox"/> JP | Japan..... | <input checked="" type="checkbox"/> US | United States of America..... |
| <input checked="" type="checkbox"/> KE | Kenya..... | | |
| <input checked="" type="checkbox"/> KG | Kyrgyzstan..... | <input checked="" type="checkbox"/> UZ | Uzbekistan..... |
| <input checked="" type="checkbox"/> KP | Democratic People's Republic of Korea..... | <input checked="" type="checkbox"/> VN | Viet Nam..... |
| | | <input checked="" type="checkbox"/> YU | Yugoslavia..... |
| <input checked="" type="checkbox"/> KR | Republic of Korea..... | <input checked="" type="checkbox"/> ZW | Zimbabwe..... |
| <input checked="" type="checkbox"/> KZ | Kazakstan..... | | |
| <input checked="" type="checkbox"/> LC | Saint Lucia..... | | |
| <input checked="" type="checkbox"/> LK | Sri Lanka..... | | |
| <input checked="" type="checkbox"/> LR | Liberia..... | | |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☒ GD Grenada.....
- ☐ IN India.....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. If, in any of the Boxes, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." [indicate the number of the Box] and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

- (i) if more than two persons are involved as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;
- (ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;
- (iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;
- (iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;
- (v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;
- (vi) if, in Box No. VI, there are more than three earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI;
- (vii) if, in Box No. VI, the earlier application is an ARIPO application: in such case, write "Continuation of Box No. VI", specify the number of the item corresponding to that earlier application and indicate at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

3. If the applicant claims, in respect of any designated Office, the benefits of provisions of the national law concerning non-prejudicial disclosures or exceptions to lack of novelty: in such case, write "Statement concerning non-prejudicial disclosures or exceptions to lack of novelty" and furnish that statement below.

Continuation of Box No. II

Novartis AG is applicant for all designated States with the exception of: AT (Austria)
US (USA)

Continuation of Box No. III

Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. is applicant for AT (Austria) only.

Box No. VI PRIORITY CLAIM☐ Further priority claims are indicated in the Supplemental Box

| Filing Date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: | | |
|---|----------------------------------|----------------------------------|---|--|
| | | national application: country | regional application:* regional Office | international application: receiving Office |
| item (1) 03 December 1997 (03.12.97) | 9725556.6 | GB | | |
| item (2) | | | | |
| item (3) | | | | |

☐ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s) :

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA)
(If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA/

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following number of sheets:

request : **5**
description (excluding sequence listing part) : **22**
claims : **2**
abstract : **1**
drawings : **-**
sequence listing part of description : **10**
Total number of sheets : 40

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: **AV 36671 + 37586**
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No VI as item(s): **(1)**
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☒ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other (specify):

Figure of the drawings which should accompany the abstract: **-**

Language of filing of the international application:

English**Box No. IX SIGNATURE OF APPLICANT OR AGENT**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

**In the name of the applicants
The representative**

M. Becker

18.11.1998**BECKER, Konrad, AV 36671 + 37586**

For receiving Office use only

1. Date of actual receipt of the purported international application:

01 DEC 1998**(- 1. 12. 98)**

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): **ISA/**

6. ☐ Transmittal of search copy delayed until search fee is paid

2. Drawings:

☐ received☐ not received:

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/07792

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/82 C12N15/52 C12N15/53 C12N9/00 C12N9/02
C12N5/10 G01N33/50 A01H5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | WO 96 10083 A (CIBA GEIGY AG) 4 April 1996 page 3,6; example 22 | 1,2,7, 13,15-17 |
| X | EP 0 497 366 A (DONEGANI GUIDO IST) 5 August 1992 pages 5,6-15,16; page 18, line 43-50; claims | 1,2,8, 13,15-17 |
| Y | WO 96 16173 A (UNIV LEEDS ; ATKINSON HOWARD JOHN (GB); MCPHERSON MICHAEL JOHN (GB)) 30 May 1996 pages 1,3,4,5,; page 6, line 16-20; page 11,22-30; claims 27-38; Table 3 | 1-4,7, 12-17 |
| | --- -/-- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 March 1999

Date of mailing of the international search report

13/04/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Holtorf, S

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 98/07792

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|------------------------|
| X | WO 94 13810 A (UNIV MELBOURNE ; ANDERSON MARILYN ANNE (AU); ATKINSON ANGELA HILARY) 23 June 1994 | 1-3, 7, 13-17 |
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07792

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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